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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,865	LEWIN ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-16 and 52-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-16 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 7/6/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 6 July 2006 in response to the Non-Final Office Action mailed 6 April 2006. Claims 1-16 were considered in the 6 April Office Action. Claims 4-6 were canceled, claims 1, 7 and 11 were amended and claims 52-56 were added in the 7 July Paper. Claims 1-3, 7-16 and 52-56 are pending and under consideration.

Response to Amendment and Arguments

Rejection of claims 4-6 is moot in view of the cancellation thereof.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 7-16 **stand rejected** and newly added claims 52-56 **are rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for the reasons set forth in the previous Office Action, beginning at page 3, and herein below in the response to Applicant's arguments.

The previous Office Action concludes, based on a careful consideration of the knowledge available to the skilled artisan at the time of filing, the teachings of the instant specification and the relevant factors as set forth in *In re Wands*:

> Although the relative level of skill in the art is high, the skilled artisan would not be able to use the claimed invention to assess the efficacy of an obesity treatment in a subject of identify a test therapeutic agent for treating obesity without first having to engage in undue experimentation to establish that expression of the OB1 gene is a valid marker for obesity and response to anti-obesity therapeutics. The art clearly establishes that putative biomarkers must be validated and that "few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation" (Feng *et al.*, *Id.*). Furthermore, the art teaches that physiological responses identified in the ob/ob mouse cannot be predictably extended to obesity in general and all species of mammal. Still further, according to Applicant's own post-filing disclosure, the practicability of the claimed invention with test cell populations other than pituitary cells remained unknown at the time of filing.
>
> Given this high degree of unpredictability and the absence of any evidence to indicate that OB1 gene expression is a valid surrogate endpoint for obesity, the basic premise underlying the claimed invention is no more than a theoretical possibility. This is not sufficient to meet the enablement requirement of 35 USC §112, first paragraph.

Bridging ¶, pp. 8-9 and first full ¶, p. 9.

Response to Arguments

At the outset, it should be made clear that the claims under consideration are directed to methods wherein expression of the OB1 gene is used as a surrogate endpoint for therapeutic efficacy in the treatment of obesity. It is further noted that the claims generally cover a methods of assessing therapeutic efficacy in treatment of obesity irrespective of etiology and wherein the test cell population can be any cell population "capable of expressing one or more nucleic acid sequences selected from the group consisting of a nucleic acid sequence that encodes a

polypeptide that comprises at least 80% homology with SEQ ID NO: 29". Therefore, the issue at hand is whether the disclosure would enable the skilled artisan to use expression of the OB1 gene as a surrogate endpoint for therapeutic efficacy as broadly claimed.

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. See MPEP 2164.03.

In the instant case, Applicant's have demonstrated that the OB1 (PC2) gene is induced in ob/ob mice as compared to litter mate controls and suppressed in ob/ob mice in response to the administration of exogenous leptin (see especially Example 10, commencing on page 72, and Table 5, page 75). Based on this, the application seeks to claim the use of PC2 gene expression in any cell of any animal to assess the efficacy of an obesity treatment in a subject and to identify agents that modulate obesity.

The Office Action cites Wagner who teaches, "A rational basis for recommending the use of a putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging the left and right columns on page 43) and "Biomarkers require validation in most circumstances"; the Office Action cites Frank *et al.* who teaches, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability

and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action"; and the Office Action cites Feng *et al.* who teaches, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation...A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models". (The 6 April Office Action, pp. 4-5.)

These teachings clearly indicate that genomic data from animal models are generally not viewed in the art as reasonably establishing that a gene is a valid marker for therapeutic effect. On the contrary, the art views the type of evidence presented in the instant application as only the first step in a process which "pose[s] great research challenges" and teaches that "few of the biomarkers showing promise in initial discovery [are] found to warrant subsequent validation".

In the discussion under the heading "Validation of biomarkers" beginning at page 11, Applicant dismisses the generally recognized unpredictability of the art. Applicant cites *In re Brana* as standing for the principle that the stage at which a biotechnological or pharmaceutical invention become useful is well before it is ready to be used in a clinical setting, and asserts that clinical approval is not a prerequisite for enablement. Applicant also cites *Cross v. Iizuka* as evidencing that a rigorous or an invariable exact correlation is not required.

These arguments have been fully considered but are not deemed persuasive. With regard to *Brana*, the Court was considering the requirements for meeting the "credible utility" prong of

35 U.S.C. §101, not enablement under 35 U.S.C. §112, first paragraph. Regarding the relationship of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, MPEP 2107.01 instructs:

> It is important to recognize that 35 U.S.C. 112, first paragraph, addresses matters other than those related to the question of whether or not an invention lacks utility...The fact that an applicant has disclosed a specific utility for an invention and provided a credible basis supporting that specific utility does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. 112, first paragraph. For example, if an applicant has claimed a process of treating a certain disease condition with a certain compound and provided a credible basis for asserting that the compound is useful in that regard, but to actually practice the invention as claimed a person skilled in the relevant art would have to engage in an undue amount of experimentation, the claim may be defective under 35 U.S.C. 112, but not 35 U.S.C. 101.

The Courts decision in *Brana* does not take into account the matters other than those related to the question of whether or not an invention lacks utility, which are relevant in the instant case because the instant claims are rejected under 35 U.S.C. §112, first paragraph, not 35 U.S.C. §101.

With regard to clinical approval, the Office has not required clinical approval. MPEP 2164.05 requires that the determination as to whether the claims are enabled be based on a consideration of the record as a whole. The previous Office Action presents a thorough analysis of the record and the factual inquiries set forth in *In re Wands* and concludes based on that analysis that the disclosure is not enabling for what is claimed. This conclusion is not based on a requirement that clinical approval be obtained.

With regard to *Cross v. Iizuka*, the Court was careful to distinguish claims directed to compounds from claims directed to therapeutic use. At page 748, the Court states, "[t]his is not a case such as *In re Gardner*, 427 F.2d 786, 166 USPQ 138 (1970), where the CCPA held that the applicant's disclosure was nonenabling because inventive skill and undue experimentation would

be required to discover approprite [sic] dosages for humans, i.e., a therapeutic use. In the instant case, we are confronted with a pharmacological activity or practical utility, *not a therapeutic use.*" (emphasis added). Thus, the Court in *Cross v. Iizuka* indicates that claims limited to a specific use are addressed by *In re Gardener*. In *In re Gardener*, the Court found that claims directed to methods of treatment or compositions claimed in terms of use are not enabled in the absence of a clear teaching of how the compositions or methods can be effectively used for the purpose set forth in the specification.

Applicant is further reminded that the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404; In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification)." *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513.

The claims in the instant case are directed to processes of assessing the efficacy of an obesity treatment based on OB1 expression. Furthermore, the claims are generic to practicing the method in any cell of any animal and encompass assessing efficacy in the treatment of obesity regardless of the etiology of the condition. It is incumbent upon the disclosure to clearly teach the skilled artisan how to practice the method as claimed, which teaching must be commensurate with the scope of protection sought. For the reasons set forth in the previous Office Action and

herein, the skilled artisan would not be able to practice what is claimed without first having to engage in undue experimentation to validate that the OB1 gene is actually a marker that can be used to assess the efficacy of an obesity treatment in a subject as broadly as is presently claimed.

In the second full paragraph on page 9, Applicant contends that the Office Action does not establish that the human response to leptin does not reasonably correlate with the animal model. In response to the Office citation of Jéquier *et al.* as teaching human obese subjects have high plasma leptin concentrations that do not induce the expected responses and that obese humans are resistant to the effects of endogenous leptin, Applicant cites Heymsfield et al., which discloses that 24 week exposure of obese subjects to leptin did result in small but significant weight loss in obese human subjects. In the paragraph bridging pp. 9-10, Applicant contends that the application discloses that the administration of leptin decreases expression of OB1 and that the down regulation of OB1 in response to leptin may contribute to the loss of the obese phenotype and contends that the results of Heymsfield et al. establish that the human response to leptin correlates with the response to leptin in the animal model.

This argument and the findings of Heymsfield et al. have been fully considered but are not deemed persuasive. It should be made clear that the relevant question is not whether any human response to leptin reasonably correlates with the response of the ob/ob mouse but whether the altered expression of OB1 in pituitary cells of an ob/ob mouse reasonably establishes that expression of OB1 in any cell from any animal can be used to assess the efficacy of an obesity treatment as broadly claimed. The claims are not directed to using leptin to treat obesity in humans. The claims are directed to using a single specific endpoint (i.e., the level of expression of the OB1 gene) as a marker of response to an obesity treatment regardless of the species or

type of cell assayed or the etiology of the obesity. Heymsfield et al. provides no evidence that OB1 expression is altered in human subjects upon treatment with leptin or any other antiobesity agent. In view of the generally unpredictable nature of the art discussed above, the findings of Heymsfield et al. cannot be construed as validation that the teachings of the instant application enable the use of OB1 expression as biomarker for efficacy in the treatment of obesity. This is particularly true in light of the other art cited in the Office Action, which clearly indicates that many responses to leptin vary among mammalian species. The Office Action cites Popovic *et al.* who teaches, "Experiments in rodents have shown that leptin activates the sympathetic nervous system, is involved in regulation of blood pressure, hematopoiesis, immune function, angiogenesis and brain, bone and pituitary development. Some biological effects expected based on observations in rodents, have so far not been seen in humans. Thus due to species differences in the role of leptin it is difficult to translated the data from rodents to human physiology"; the Office Action cites Jéquier *et al.*, who concludes based on several lines of evidence that leptin acts as a satiety factor in mice but not in humans; and the Office cites Gorden *et al.*, who teaches that leptin accelerates the onset of puberty in normal mice but does not induce puberty in humans and teaches, "[Leptin] was discovered in a rodent model; these models have been important guides in further understanding leptin physiology. There might be differences among rodent models, however, as a result of the quantitative severity of the phenotype and genetic background. Therefore, rodent models might not predict the human physiological or pharmacological response to leptin administration."

Given the complexity and disparate nature of the response to leptin in mammals, the data presented by Heymsfield et al. evidencing some weight loss in obese humans treated with leptin

for extended periods does not reasonably establish that OB1 expression in any cell from any mammal can be used as a marker for antiobesity drug efficacy.

In the first full paragraph on page 10, Applicant dismisses the teachings of Gordon et al. and Popovic et al. as moot in view of the teachings Heymsfield et al., which clearly demonstrates that administration of exogenous leptin to obese human subjects induces weight loss. However, it is again noted that the claims are not directed to a method of inducing weight loss by administering leptin. The claims are directed to using OB1 expression in any cell of any animal as a marker for clinical efficacy in the treatment of obesity, regardless of the cause of obesity. Outside of pituitary cells of the ob/ob mouse treated with leptin, there is no evidence for alterations in OB1 gene expression associated with obesity or antiobesity treatment. What the teachings of Gordon et al. and Popovic et al. clearly show is that one cannot assume that every response to leptin in an ob/ob mouse also occurs in other animals and in forms of obesity that do not result from the complete absence of leptin as is the case in the ob/ob mouse.

In the following paragraph, Applicant contends that the teachings of Takahashi et al. actually validate that exogenous administration of leptin in mice induces weight loss regardless of whether the mice express or do not express endogenous leptin. Applicant contends that, in view of this, that the response to leptin in humans correlate with the response of mice to leptin and the upregulation of PC2 in ob/ob mice in response to leptin indicates PC2 can serve as a biomarker for obesity.

As described in the previous Office Action, Takahashi et al. teaches that there are significant variations in the physiological responses to leptin even among different strains within the *same species*. Thus, the teachings of Takahashi evidence the unpredictable nature of

extending the findings of OB1 expression in the pituitary cells of the ob/ob mouse to the use of OB1 expression in any cell of any animal as a biomarker for efficacy in the treatment of obesity of any etiology as broadly claimed. In view of the teachings of Takahashi et al. and the record as a whole, the skilled artisan would clearly conclude that one would not be able to practice the invention as broadly claimed without undue experimentation in order to validate that the method is enabled for the full scope or to identify the enabled embodiments within the scope of the claims.

The Office Action cites Naggert *et al.* as reporting that, unlike the ob/ob mouse used in the instant working examples wherein expression of the OB1 gene (known in the art as PC2) was elevated relative to littermate controls, there was no change in the expression of PC2 in fat/fat obese mice relative to littermate controls[1]. In view of this, the Office asserts that the general applicability of OB1 expression as a marker for obesity and responsiveness to agents that affect obesity is clearly unpredictable.

In response, Applicant acknowledges Naggert et al. teaches that there is no change in the amount of PC2 associated with obesity as measured by western blot in the fat/fat mouse but dismisses this teaching on the grounds that no actual data are shown and no quantitative or semiquantitative techniques were used to establish that there was no increase in PC2. Applicant also asserts that an absence of a change in PC2 activity seemingly contradicts the results showing an increase in the number of immature β-granules.

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[1] The Office Action mistakenly indicates this teaching is found at column 2, lines 45-65 while it is actually at column 10, lines 45-65.

This argument has been fully considered but is not deemed persuasive. Naggert et al. unequivocally teaches that Western blot results obtained for PC2 showed that the enzyme was "present in equal amounts in the lysates of both [wild-type and fat/fat] genotypes." (Col. 10, ll. 64-65). In contrast to Applicant's assertion, Western blotting is recognized in the art as a quantitative assay and there is no reason of record to doubt the objective truth of the teachings of Naggert et al. With regard to the "increase in immature β-granules", Naggert et al. actually teaches, "In contrast to an abundance of mature granules with electron dense cores in +/+ controls, fat/fat β cells exhibited a preponderance of the more electron-lucent immature granule forms..." (Col. 10, ll. 36-39.) Naggert et al. does not teach that there is an overall increase in the number of immature granules but that the immature form is predominant in the fat/fat mouse. This might result from an increase in the number of immature granules, a decrease in the number of mature granules or both. Naggert et al. postulates that the difference in fat/fat mice is due to an impairment in proinsulin processing (col. 10, ll. 35-42), which would actually be more consistent with a decrease in PC2 than an increase in the enzyme. However, Naggert et al. also explains the decrease in processing by showing a loss of enzymatically active CPE in β-cells. (Col. 10, ll. 43-55.) Viewed as a whole, the EM data provide no reason to doubt the objected truth of the Western blot results presented by Naggert et al., which are based a direct quantitative determination of the amount of PC2 enzyme present.

Finally, in support of the contention that, at the time of filing, test cell populations that could be used in the claimed method, other than pituitary cells, remained to be identified, the Office cites Applicant's own statement in Renz *et al.*, which teaches, "We do not yet know whether the effect of leptin on *PC2* expression is limited to particular cell types" (second

paragraph on page 10433). In response, Applicant merely contends that one of ordinary skill in the art would be able to use any cell that expresses an endogenous POMC or PC2 and any cell type can be used to express a recombinant PC2.

This argument has been fully considered but is not deemed persuasive. Practicing the claimed method requires not only that PC2 be expressed in a given cell type but that the effect of leptin and other pharmaceutical agents on PC2 expression correlate with the ability of those agents to act as antiobesity drugs. Renz *et al.* teaches that it is unknown whether the effect of leptin on PC2 expression is limited to particular cell types. In view of this, one of skill in the art at the time of filing would clearly not know which PC2 expressing cells provide an accurate measure of a compounds antiobesity activity. Therefore, the skilled artisan must determine experimentally which cells can be used in the method as claimed.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-16 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06.) The MPEP further states, "[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

In the instant case, Applicant has amended the claims to recite that the cells used in the assay are "capable of expressing a nucleotide sequence that encodes a polypeptide that comprises at least 80% sequence homology with SEQ ID NO: 29 and has the activity of a prohormone convertase", or hybridizes to SEQ ID NO: 28 under stringent conditions. Applicant has also amended the specification, which did not previously disclose SEQ ID NO: 28 or SEQ ID NO: 29, to include the sequence data. In support of these amendments, Applicant cites Table 2, which

references Genbank accession no. M55669. The cited Genbank accession number discloses the nucleic acid sequence set forth as SEQ ID NO: 28 and, as Applicant points out in the Remarks, M55669 references AAA39376, which discloses the polypeptide sequence set forth as SEQ ID NO: 29. (Remarks, p. 8, ¶3.)

It appears that Applicant views the citation of the Genbank accession number as an incorporation by reference and has amended the specification and claims to recite essential subject matter disclosed therein. However, Applicant is reminded that a mere reference to material does not convey an intent to incorporate the material by reference. See 37 CFR 1.57(g)(1). Furthermore, any incorporation by reference must clearly identify the material to be incorporated. See *In re de Seversky*, 474 F.2d 671, 674(C.C.P.A. 1973) (incorporating document must "clearly identify[ ] the subject matter which is incorporated and where it is to be found"), cited at M.P.E.P. § 608.01(p); see also *Advanced Display Sys., Inc. v Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.").

In the instant case, Table 2 of the specification merely refers to the accession number as among the "Nucleic Acid Sequences Discussed Herein". There is no statement that clearly identifies any material disclosed in the accession number as incorporated by reference. In particular, the statement makes no reference at all to the polypeptide sequence disclosed in accession no. AAA39376. Therefore, even if Table 2 had contained an explicit statement that the cited nucleic acid sequences are incorporated by reference, the incorporation by reference would not support amendment of the specification and claims to refer to SEQ ID NO: 29.

In view of the foregoing, the skilled artisan would conclude that the disclosure as originally filed does not provide descriptive support for a nucleic acid comprising SEQ ID NO: 28 or a polypeptide comprising SEQ ID NO: 29. Therefore, the amendments to the specification and claims constitute impermissible new matter.

In addition, even if a proper incorporation by reference had been made, the amendment is improper because it is not accompanied by a statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter as required under 37 CFR 1.57(f).

Claims 1-3, 7-16 and 52-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, the claims to recite that the cells used in the assay are "capable of expressing a nucleotide sequence that encodes a polypeptide that comprises at least 80%

sequence homology with SEQ ID NO: 29 and has the activity of a prohormone convertase", or hybridizes to SEQ ID NO: 28 under stringent conditions and has the activity of a prohormone convertase. Furthermore, the claims 54 and 55 explicitly recite that the variant sequences are "naturally occurring". Thus, the claims embrace a method of using a broad genus of nucleic acids encoding polypeptides having prohormone convertase activity and claim the use of naturally occurring (i.e., allelic) variants.

The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

In the instant case, the nucleic acid sequence of the claims is clearly a critical element of the claimed method as it is the expression of the nucleic acid that determines the outcome recited in the method. Therefore, the written description of the nucleic acid must meet the requirements of 35 U.S.C. §112, first paragraph.

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (Federal Register, Vol. 66, No. 4, Column 3, page 1106). "The written description

requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)).

In the instant case, the nucleic acid sequence comprising SEQ ID NO: 28 and encoding SEQ ID NO: 29 are described solely by reference to a Genbank accession number disclosing a single species of nucleic acid within the scope of the nucleic acid of the claims. In the remarks filed 6 July 2006, Applicant also cites Accession numbers that disclose the human PC2 nucleic acid sequence. While these citations evidence that certain species within the scope of the claims were conventional in the art at the time the application was filed, they do not support a genus of nucleic acids encoding any polypeptide having 80% homology with SEQ ID NO: 29 and the activity of a prohormone convertase. The specification fails to set forth the relevant structural characteristics of the nucleic acid such that the skilled artisan could distinguish those nucleic acids having the function recited in the claims from those nucleic acids that do not have that function. Thus, outside of the nucleic acids that were conventional in the art at the time of filing, the specification fails to convey the relevant, identifying characteristics of the claimed invention sufficient to show possession of the genus.

With regard to naturally occurring allelic variants, the specification provides no description of how the structure of the nucleic acids cited relate to the structure of any strictly neutral alleles. The general knowledge in the art concerning alleles does not provide any

indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. As the common attributes of the subgenus of naturally occurring allelic variants are not described, one of skill in the art would conclude that applicant was not in possession of the full scope of the invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of any nucleic acid nucleic acid having the properties recited in the claims.

Specification

The 7 July amendment is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment of the specification and sequence listing to recite the sequences set forth as SEQ ID NO: 28 and 29 introduces impermissible new matter for the reasons set forth herein above.

Applicant is required to cancel the new matter in the reply to this Office Action.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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